Patent Foramen Ovale and the Risk of Cerebral Infarcts in Acute Pulmonary Embolism—A Prospective Observational Study

David Vindiš, MD,* Martin Hutyra, PhD,* Daniel Šaňák, PhD,† Michal Král, PhD,† Eva Čecháková, PhD,‡ Simona Littnerová, MSc,§ Tomáš Adam,‖ Jan Přeček, MD,* Štěpán Hudec, MD,* Markéta Ječmenová, MD,* and Miloš Táborský*

Background: Pulmonary embolism (PE) is associated with a risk of consecutive paradoxical embolism with brain infarction through a patent foramen ovale (PFO). The aims of this study were to assess the rate of new ischemic brain lesions (IBLs) using magnetic resonance imaging (MRI) during a 12-month follow-up period with anticoagulation and to evaluate the potential relationship with the presence of PFO on transesophageal echocardiography (TEE). *Subjects and Methods:* Seventy-eight patients with acute PE underwent baseline contrast TEE with brain MRI. After the 12-month follow-up, 58 underwent brain MRI. The rates of MRI documenting new IBLs were measured based on the presence of PFO. *Results:* PFO was detected in 31 patients (39.7%). At baseline MRI, IBL was present in 39 of 78 patients (50%). The presence of IBL was not significantly higher in patients with PFO than in patients without PFO (20 [64.5% patients with PFO] versus 19 [40.4% without PFO] of 39 patients with baseline IBL, $P = .063$).At the follow-up MRI, in the group with new IBL (9 of 58 patients, 15.5%), the number of patients with PFO was significantly higher than that without PFO (7 [33.3%] versus 2 [5.4%], $P = .008$). PFO was identified as an independent predictor of new IBL (odds ratio 4.6 [1.6-47.4], $P = .008$). *Conclusions:* The presence of PFO was associated with new IBL in patients with PE. These patients are at a higher risk of ischemic stroke despite effective anticoagulation therapy. **Key Words:** Pulmonary embolism—patent foramen ovale—brain infarction—echocardiography—brain magnetic resonance imaging.

From the *Department of Internal Medicine I—Cardiology; †Comprehensive Stroke Center, Department of Neurology; ‡Department of Radiology, University Hospital and Faculty of Medicine and Dentistry, Palacký University, Olomouc, Czech Republic; §Institute of Biostatistics and Analyses at the Faculty of Medicine and the Faculty of Science, Masaryk University, Brno, Czech Republic; and ‖Department of Clinical Biochemistry, University Hospital and Faculty of Medicine and Dentistry, Palacký University, Olomouc, Czech Republic.

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Address correspondence to Martin Hutyra, MD, PhD., FESC, Department of Internal Medicine I—Cardiology, University Hospital and Faculty of Medicine and Dentistry, Palacky University, I. P. Pavlova 6, 77900 Olomouc, Czech Republic. E-mail: martinhutyra@seznam.cz.

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Introduction

A patent foramen ovale (PFO) is a known risk factor for paradoxical embolism, including ischemic stroke (IS).[1] However, the closure of a PFO has been still discussed controversially. The results of trials and recent meta-analyses showed a trend to a favorable effect of the closure as a secondary prevention of IS.[2,3]

Paradoxical embolism has been observed in patients with acute pulmonary embolism (PE) with coexisting PFO, and PFO has been reported to be a significant predictor of poor outcome in this group.[4]

Clinically silent ischemic brain embolisms were detected in patients with PE and PFO, especially in patients with significant right ventricular (RV) dysfunction leading to right-to-left interatrial shunt via PFO in the acute phase of PE.[4-6]

Magnetic resonance imaging (MRI) enables the reliable detection of ischemic brain lesions (IBLs); moreover, the use of diffusion-weighted MRI allows the sensitive detection of acute cerebral ischemia.

Aims

The aims of our prospective study were to assess the rates of new IBLs detected on MRI and clinical IS events in patients with present acute PE during a 12-month follow-up period (FUP) on effective oral anticoagulation therapy (OAT) and to evaluate a potential relationship with the presence of PFO on transesophageal echocardiography (TEE).

Subjects and Methods

A prospective observational single-center study was conducted. Seventy-eight consecutive patients with acute PE were enrolled between the years 2011 and 2013.

Acute PE was confirmed with clearly positive findings on computed tomography (CT) angiography of the pulmonary arteries.

To be included in this prospective study, patients had to have a certified diagnosis of first unprovoked acute PE documented by the performance a pulmonary CT scan. Additionally, inclusion criteria were written consent, age 18 years or older, consent with contrast TEE and brain MRI, negative magnetic resonance cerebral angiography, and carotid ultrasound. Exclusion criteria were contraindications to MRI, TEE, previous OAT, and left atrial, ventricular, or valvular source of cerebral embolism on TEE.

All patients signed an informed consent before enrollment. The study was approved by the local ethics committee of our institution.

Based on the balance between the risk of recurrence of PE and that of bleeding, patients with a first unprovoked PE and a low risk of bleeding were treated with indefinite OAT for at least 12 months, consistently with the patient's preference.[7]

At baseline, all patients (N = 78) underwent contrast TEE and brain MRI (Fig 1).

At the follow-up visit, all patients (N = 58) underwent contrast transthoracic echocardiography (TTE) and control brain MRI. Twenty patients were lost to follow-up (8 died, 7 experienced IS, and 5 refused to participate).

Based on the presence of PFO, the patients were divided into 2 subgroups (PFO presence or absence). The presence of new IBL on control MRI and the presence of clinical IS events were compared between the groups at baseline and at the end of follow-up.

Echocardiography

TTE was performed with a Vivid 7 machine (GE Healthcare Technologies, Waukesha, WI) with an M3S probe (2-5 MHz) and focused on the echocardiographic probability of pulmonary hypertension on the first day of hospitalization and after a 12-month FUP.

RV morphology and longitudinal systolic function were quantified using parameters obtained from an apical 4-chamber view: tricuspid annular plane systolic excursion (measured in millimeter) and peak tricuspid annulus systolic velocity (S', measured in centimeter per second).[7,8]

TEE was performed during the first week of hospitalization with a Vivid 7 machine with a TEE 6T probe (2.9-7.0 MHz) and focused on PFO, left-to-right and right-to-left shunts (RLS), atrial septum aneurysm (ASA), and right heart transient thrombi to exclude potential cardiac or vascular sources of embolization.

PFO was diagnosed by visualizing left-to-right, right-to-left, or bidirectional shunting using color Doppler with a TEE midesophageal bicaval view. An echo-contrast agent (colloidal solution of 6% hydroxyethyl starch) applied through a peripheral venous catheter, in combination with a Valsalva maneuver, was used. A PFO was present if microbubbles were visualized within the left heart within 3 cycles of maximal right atrium contrast opacification.

A detailed evaluation was done off-line in the Echopac 7 Option program (GE Healthcare, Little Chalfont, United Kingdom) (BT 10.0.0 version) by 2 independent examiners who were blinded to the results of other examinations.

Magnetic Resonance Imaging

Brain MRI was performed during the patient hospitalization for qualifying acute PE and after a 12-month FUP using a Magnetom Symphony 1.5 T Maestro Class (Siemens, Erlangen, Germany) scanner. The protocol contained the following sequences: (1) T2-weighted turbo spin echo, (2) fluid-attenuated inversion recovery (FLAIR), (3) diffusion-weighted imaging (DWI), and (4) 3D time-of-flight magnetic resonance angiography (MRA).

The imaging analysis was performed by an experienced neuroradiologist blinded to the clinical and